NOT FOR PUBLICATION

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

PROMETHEUS LABORATORIES INC.,	:	Civil No. 11-230 (FSH) Civil No. 11-1241(FSH)
Plaintiff,	:	
v.	:	**OPINION**
ROXANE LABORATORIES, INC., et al.,	:	
Defendants.	:	September 23, 2013

HOCHBERG, District Judge

This case comes before the Court on requests for claim construction from Plaintiff Prometheus Laboratories Inc., ("Prometheus" or "Plaintiff") together with Defendants Roxane Laboratories, Inc. and Cipla Ltd. (collectively "Defendants"). The parties submitted their Joint Claim Construction and Prehearing Statement on October 21, 2011. On December 9, 2011, the parties filed their opening claim construction briefs, and on February 10, 2012, they filed their responsive briefs. The parties filed a second Joint Claim Construction and Prehearing Statement on February 21, 2012. On March 9, 2012, the parties filed a second set of opening claim construction briefs, and on April 9, 2012, they filed their responsive briefs. On October 11, 2012, the parties amended their Joint Claim Construction and Prehearing Statement. A *Markman* hearing took place on October 17, 2012. The parties again amended their Joint Claim Construction and Prehearing Statement on August 7, 2013.

I. BACKGROUND

These cases arise out of actions for patent infringement under the Federal Food, Drug, and Cosmetics Act ("FFDCA"), and, more specifically, the Hatch-Waxman Amendments to that law. Prometheus is the owner of U.S. Patent No. 6,284,770 (the "'770 patent") and U.S. Patent No. 6,175,014 (the "'014 patent").

On September 4, 2001, the United States Patent and Trademark Office ("USPTO") issued the '770 patent, "Medicaments for the treatment of non-constipated female irritable bowel syndrome." The '770 patent was thereafter subject to reexamination proceedings before the USPTO which resulted in the cancellation or amendment of all of the original claims of that patent. On October 19, 2010, the USPTO issued a reexamination certificate for the '770 patent.

Prometheus holds an approved New Drug Application ("NDA") under § 505(a) of the FFDCA, 21 U.S.C. § 355(a), for alosetron hydrochloride tablets (NDA No. 21-107), selling under the brand name LOTRONEX®. The reexamined claims of the '770 patent cover the methods of use and administration of alosetron or a pharmaceutically acceptable derivative thereof. After reexamination, the '770 patent was listed in the U.S. Food and Drug Administration ("FDA") publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to LOTRONEX®.[1]

Background of the '770 Patent

This case arises out of Roxane's filing of ANDA No. 200-652 with the FDA, which seeks approval to market a generic version of Prometheus' LOTRONEX® product. The active ingredient in LOTRONEX® is alosetron hydrochloride. Prometheus alleges, *inter alia*, that under 35 U.S.C.

[1] The FDA lists the patent numbers in the Orange Book that the NDA applicant identifies as being associated with that NDA.

§ 271(e)(2) Roxane's submission of ANDA No. 200-652 to the FDA constitutes infringement of the claims of reexamined '770 patent owned by Prometheus. Roxane alleges, *inter alia*, that the asserted claims are invalid and/or not infringed. The parties have identified six disputed claim terms.[2]

LOTRONEX® was developed by Glaxo Wellcome, Inc. (currently d/b/a GlaxoSmithKline, hereinafter "GSK") and first approved by the FDA on February 9, 2000. Following its initial approval, some LOTRONEX® patients experienced severe adverse events, which in some cases were followed by hospitalization for fecal impaction, intestinal obstruction, ischemic ulceration of bowels, and gangrenous colitis. Due to safety concerns, it was withdrawn from the market in November 2000. LOTRONEX® was reintroduced to the market in late 2002 after safety features/protocols were implemented. It was decided that LOTRONEX® would have to be distributed under a Risk Evaluation and Mitigation Strategy (REMS) that incorporated the methods described in the '770 patent. The LOTRONEX® REMS is known today as the Prescribing Program for LOTRONEX®. In 2007, Prometheus acquired LOTRONEX® and the '770 patent.

Roxane claims that during reexamination, Prometheus and its patent attorneys, without the involvement of the inventors, proposed amendments to the original '770 patent claims adding words and phrases allegedly supported by the specification of the '770 patent. Roxane further argues that these added words and phrases bear little, if any, relationship to the subject matter described in the specification of the '770 patent. Roxane contends that, according to Prometheus, the limitations added to the amended claims corresponded to the changes GSK

[2] In the Joint Claim Construction Statement, the parties identified seven disputed claim terms. However, after the statement was filed Roxane withdrew its proposed construction of the term "assessing." Roxane now agrees with Prometheus that "assessing" has a well understood ordinary meaning that requires no additional construction.

made to the LOTRONEX® label in conjunction with the reintroduction of LOTRONEX® in 2002—changes GSK made to the label long after the filing of the original '770 patent specification and after the issuance of the '770 patent.

Background of the '014 Patent

This case arises out of Roxane's filing of ANDA No. 200-652 with the FDA, which seeks approval to market a generic version of Prometheus' LOTRONEX® product. Defendant Cipla Ltd. imports alosetron hydrochloride into the U.S. for use as the active pharmaceutical ingredient in Roxane's generic version of LOTRONEX®. On November 18, 2011, Prometheus filed its First Amended Complaint alleging, among other things, that Roxane will infringe the '014 patent under 35 U.S.C. § 271(g) by using, offering to sell, importing, and/or selling alosetron hydrochloride, and/or Roxane's ANDA products containing alosetron hydrochloride, manufactured by a process that infringes the '014 patent in the U.S. Roxane alleges, *inter alia*, that the asserted claims are not infringed.

II. DISCUSSION

A. Standard of Review

In a patent infringement analysis, the first step is to define the meaning and scope of the claims of the patent. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). The construction of patent claims is a matter of law reserved exclusively for the court. *Markman*, 52 F.3d at 977-79. There are two categories of evidence available to the Court when construing patent claims: (i) intrinsic evidence; and (ii) extrinsic evidence, such as expert testimony.[3] "When construing a claim, a court principally

[3] The use of extrinsic evidence is limited in purpose and scope.

consults the evidence intrinsic to the patent, including the claims, the written description, and any relevant prosecution history." *Mantech Environmental Corp. v. Hudson Environmental Services, Inc.*, 152 F.3d 1368, 1371 (Fed. Cir. 1998); *see also Markman*, 52 F.3d at 979 ("To ascertain the meaning of claims, we consider three sources: The claims, the specifications, and the prosecution history.").

The court's analysis must begin with the language of the claims themselves, "for it is that language that the patentee chose to use to 'particularly point[] out and distinctly claim[] the subject matter which the patentee regards as his invention.'" *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001) (quoting 35 U.S.C. § 112, ¶ 2). Claims are "examined through the viewing glass of a person skilled in the art" as of the effective date of the patent, and claim terms are deemed to be read "not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). When a patentee specifically defines a claim term in the specification, it is that definition that controls. *Id.* at 1316. When the patentee has not provided an explicit definition of a claim term, the words of a claim are given their plain and ordinary meaning to a person of ordinary skill in the art. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

To determine how a person of skill in the art would understand a patent's claim language, a court must first examine the intrinsic record, *i.e.*, the patent itself, including the claims, the specification and the prosecution history. *Id.* (citing *Markman*, 52 F.3d at 979). The specification "acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Id.* The Federal Circuit has explained that the specification is

"usually . . . dispositive . . . [and is the] best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (quoting *Vitronics*, 90 F.3d at 1582) (internal quotations omitted). Therefore, a court should "rely heavily on the written description for guidance as to the meaning of the claims." *Id*. at 1317.

A patent's prosecution history is another useful source of guidance, as it "provides evidence of how the PTO and the inventor understood the patent." *Id.* The prosecution history is the complete record of the proceedings before the USPTO, and "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id*. The Federal Circuit has made clear the need to consult the prosecution history to "exclude any interpretation that was disclaimed during prosecution." *See Rhodia Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005) (the prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was either disclaimed or disavowed during prosecution).

If the ambiguities of a disputed claim term have not been resolved after analysis of the intrinsic evidence, a court may also consider extrinsic evidence. *Vitronics*, 90 F.3d at 1582-83. While a court may rely on extrinsic evidence to construe a claim, "what matters is for the court to attach the appropriate weight to be assigned to those sources." *Phillips*, 415 F.3d at 1324. Extrinsic evidence ordinarily should not contradict intrinsic evidence. *Id*. at 1322-23.

B. Analysis

1. Claim Construction Regarding U.S. Patent No. 6,284,770

a. Claim 5 of the '770 Patent[4]

Claim 5 states:

> A method for treating a diarrhea-predominant female IBS[5] patient, while **excluding those with predominant constipation**, said method comprising:
> assessing whether said diarrhea-predominant female IBS patient has **experienced symptoms for at least six months**; and
> **administering** an effective amount of alosetron or a pharmaceutically acceptable derivative thereof to said patient who has experienced symptoms for at least six months,
> wherein said effective amount is dependent on the condition of the patient and is at the discretion of the attendant physician.

1. "**excluding those with predominant constipation**"

The Court finds that the term "excluding those with predominant constipation" should be construed as "excluding those female IBS patients with predominant constipation." Claim 5 uses the pronoun "those" to refer back to "female IBS patient[s]" and repeats the word "predominant" which logically and in context means a "constipation-predominant" female IBS patient to distinguish it from the "diarrhea-predominant" term in the prior clause.

2. "**experienced symptoms for at least six months**"

The Court finds that the term "experienced symptoms for at least six months" means that the patient has experienced symptoms of diarrhea-predominant IBS for at least 6 months. "At least six months" means "six months or more, but not less." The Court's construction is supported by the claim language, specification, and prosecution history. As seen in context of the claim language itself, the patient is a "diarrhea-predominant female IBS patient." By definition, a "diarrhea-predominant female IBS patient" experiences symptoms of diarrhea-predominant IBS, not some other kind of IBS. This is confirmed by the prosecution history. For

[4] All three of the terms in dispute in claim 5 also appear in claim 13 of the '770 Patent.

[5] Irritable bowel syndrome.

example, both the patentees and the examiner consistently referred to the claimed "symptoms" lasting for six months as symptoms of IBS-D ("diarrhea-predominant IBS"). The claims and other intrinsic evidence demonstrate that the symptoms according to the claims are symptoms of diarrhea-predominant IBS. Accordingly, the Court construes "experienced symptoms for at least six months" to mean the patient has "experienced symptoms of diarrhea-predominant IBS for 6 months or more, but not less."

3. "**administering**"

The Court finds that the term "administering" requires no further construction as it has a well-understood meaning to persons of ordinary skill in the art. The claim language, as well as the patent specification, say nothing to cause this Court deviate from the ordinary meaning of "administering," in the context of a case about medicine, which is not limited to solely "applying onto or into" a patient, but also includes "to mete out," "to give," "to make application of," "to supervise the formal taking of," and "to bring into use or operation." The term "administering" has a well-understood meaning to persons of ordinary skill in the art and no alternative meaning is suggested by the claim language, the patent specification, or the reexamination of the '770 patent. Accordingly, "administering" requires no further construction as it has a well-understood meaning to persons of ordinary skill in the art.

B. Claim 11 of the '770 Patent[3]

Claim 11 states:

> The method for treating according to claim 5, wherein said female IBS patient experiences **improvement in stool consistency**, **bowel movement frequency** and **the proportion of days with urgency** while being treated with alosetron.

[3] All three of the terms in dispute in claim 11 also appear in claim 15 of the '770 Patent.

1. "**Improvement in stool consistency,**" "**improvement in . . . bowel movement frequency,**" & "**improvement in . . . the proportion of days with urgency**"

The parties dispute whether or not the terms "improvement in stool consistency," "improvement in . . . bowel movement frequency," and "improvement in . . . the proportion of days with urgency" are claim limitations and should be construed.

"A whereby[6] clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited." *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) (citing *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1172 (Fed. Cir. 1993)). Mere "laudatory" terms "characterizing the result of the executing step" are not limiting. *Id*. "However, when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005). This is the case when the clause "is more than the intended result of a process step" and "is part of the process itself" or "an integral part of the invention." *Id*. at 1330. Whether a clause merely states the intended result of a process or is a condition "material to patentability" is determined on a case-by-case basis. *See Shire LLC v. Amneal Pharms., LLC*, CIV. A. 11-3781 SRC, 2013 WL 4045622, at *19-20 (D.N.J. Aug. 8, 2013).

Claim 5 of the '770 patent is an independent claim describing "a method for treating a diarrhea-predominant female IBS patient." ('770 patent at claim 5.) Claim 11 depends from

[6] Claim 11 of the '770 patent uses the term "wherein" rather than "whereby" to introduce these "improvement" terms. District courts and the Manual of Patent Examining Procedure ("MPEP") apply this line of cases to other similar terms including "wherein." *See, e.g.*, MPEP § 2111.04, 8th ed., rev. 9, Oct. 2012.

claim 5 and includes three "improvement" phrases. ('770 patent at claim 11.) These phrases need construction if they are "part of the process itself" or "an integral part of the invention." *Hoffer*, 405 F.3d at 1330. But if these phrases merely describe the intended results of claim 5, then they need no construction. *Minton*, 336 F.3d at 1381.

Claim 11 of the '770 patent does not contain any obvious "steps" or additional "processes." Rather, claim 11 describes what "said female IBS patient"[7] "experiences"—namely, "improvement in stool consistency, bowel movement frequency and the proportion of days with urgency." ('770 patent at claim 11.) In claim 11, these improvements occur "while being treated with alosetron." ('770 patent at claim 11.)

The '770 patent's specification also fails to describe any "step" or "process" associated with the phrase "improvement in stool consistency, bowel movement frequency and the proportion of days with urgency."[8] These terms are never explicitly defined in the '770 patent's specification. The specification of the '770 patent does contain a section titled "Improvement in Bowel Habits." ('770 patent at 6:40.) But this section of the specification only describes the results of treating female patients with alosetron. The specification refers to these

[7] "[S]aid female IBS patient" refers to the diarrhea-predominant female recited in claim 5.

[8] Prometheus argues that because the claims at issue target IBS-D patients and diarrhea is characterized by watery and/or loose stools, an improvement in stool consistency for an IBS-D patient is to reduce watery and/or loose stools. But this argument focuses on the intended results of a treatment and fails to identify any steps added to the treatment itself. In Prometheus' most recent letter (Dkt. No. 216 (11-cv-230); Dkt. No. 330 (11-cv-1241)), it appears to argue that claim 11 is limited to a subset of female IBS-D patients—those with all three symptoms listed in claim 11. But the claim does not list the step of identifying female IBS-D patients with these three symptoms. Claim 11 only notes that the diarrhea-predominant female "experiences improvement in stool consistency, bowel movement frequency and the proportion of days with urgency." Under Prometheus' reading of the claim, the same exact steps from claim 5 could be followed and infringement under claim 11 would depend solely on the reaction of the patient to the administration of the drug.

"improvements" as "results." ('770 patent at 6:53-54.) But a "statement of the intended result of administering those amounts does not change those amounts or otherwise limit the claim." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001). In *Bristol-Myers*, the Federal Circuit found that the phrase "[a] method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity" was "only a statement of purpose and intended result" and that it did not result in "a manipulative difference in the steps of the claim." *Id*. at 1375-76. Here, any "improvement" stated in claim 11 similarly does not add "a manipulative difference in the steps of the claim."

There is also no indication that the phrase "improvement in stool consistency, bowel movement frequency and the proportion of days with urgency" was added to distinguish prior art or overcome a patent examiner's rejection during the prosecution of the '770 patent.

The Court finds that claim 11 describes the intended or hoped for results of treating a diarrhea-predominant female IBS patient with alosetron. The phrase "improvement in stool consistency, bowel movement frequency and the proportion of days with urgency" fails to add any additional steps to the method recited in claim 5 and is not "an integral part of the invention." *Hoffer*, 405 F.3d at 1330. As these phrases are merely laudatory and describe desired results, there is no need to construe them.

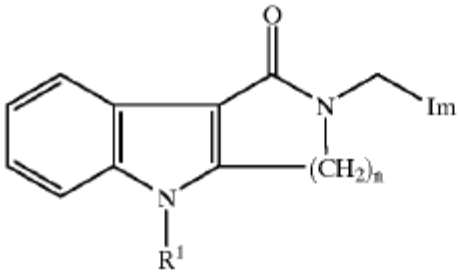
2. Claim Construction Regarding U.S. Patent No. 6,175,014

A. Claim 1 of the '014 Patent

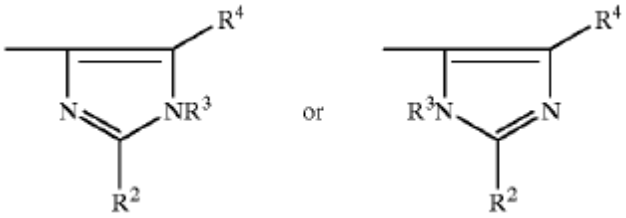
Claim 1 states:

A **process for the preparation of a compound of formula (I)**:

(I)

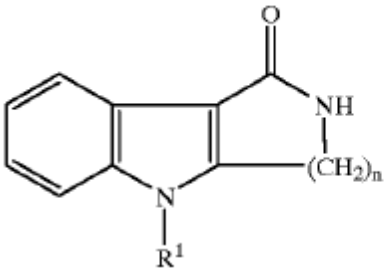


wherein Im represents an imidazolyl group of the formula:



and R^1 represents a hydrogen atom or a methyl, ethyl, n-propyl, or isopropyl group, R^2 and R^3 each represent a hydrogen atom, R^4 represents a methyl group; and n represents 2; or a physiologically acceptable salt or solvate thereof; which comprises **reacting a compound of formula (II)**

(II)



or a protected derivative thereof, with a compound of formula (III):

$HOCH_2$ -Im (III)

or a salt thereof in the presence of an acid which is a strong mineral acid or a hydrocarbylsulphonic acid at a temperature of from 100 to 200°C in a high boiling polar solvent, followed where necessary by removal of any protecting groups.

1. "**process for the preparation of a compound of formula (I)**"

While this claim term was included in Prometheus' opening *Markman* brief as a term that Roxane sought to be construed, Roxane does not include it in its *Markman* briefs, nor do the parties include it in their Joint Claim Construction chart. Accordingly, the Court need not construe this term.

2. "**reacting a compound of formula (II) . . . or a protected derivative thereof, with a compound of formula (III) . . . or a salt thereof in the presence of an acid . . . at a temperature of from 100 to 200°C in a high boiling polar solvent**"

(a) "reacting"

The Court construes "reacting" to mean "causing to undergo chemical reaction between or among." This is the plain and ordinary meaning to one of skill in the art based on the language of the claims as well as the specification of the '014 patent.

(b) "a compound of formula (II) . . . or a protected derivative thereof" and "a compound of formula (III) . . . or a salt thereof"

The Court finds that these terms have well-understood ordinary meanings to persons of ordinary skill in the art. "A compound of formula (II) . . . or a protected derivative thereof" and "a compound of formula (III) . . . or a salt thereof" both are defined by their chemical structures which are set forth in the specification and claims of the '014 patent. They require no additional interpretation or construction for a person of ordinary skill in the art.

(c) "in the presence of an acid" and "in a high boiling polar solvent"

The Court finds that the terms "in the presence of an acid" and "in a high boiling polar solvent" mean "a strong mineral acid or a hydrocarbylsulphonic acid is present when the reaction is at a temperature between 100°C and 200°C in a high boiling polar solvent." The Court's construction is supported by the language of the claim as well as the specification. The

specification notes "[t]he present invention . . . comprises reacting a compound of formula (II) … with a compound of formula (III) . . . in the presence of an acid. . . ." ('014 patent at 2:1-23.) Claim 1 describes "reacting a compound of formula (II) . . . with a compound of formula (III) . . . in the presence of an acid." It also describes "reacting a compound of formula (II) . . . with a compound of formula (III) . . . in a high boiling polar solvent." ('014 patent at claim 1.) The ordinary meaning of that phrase means that the reaction occurs "in an acid" and "in a high boiling polar solvent." Similarly, the description of the invention and the examples disclosed in the specification describe the presence of acid and high boiling polar solvents during the reaction. ('014 patent at 2:22, 2:32-34, 2:47-53, 4:18-6:52.) Furthermore, during the prosecution of the '014 patent, the patent applicant stated that "the acid present during the reaction . . ." and also said "the reaction is carried out in a high boiling polar solvent."[9] (Dkt. No. 117-1, Ex. F.)

(d) "at a temperature of from 100 to 200°C"

The Court construes "at a temperature of from 100 to 200°C" to mean "at a temperature between 100°C and 200°C, inclusive of 100°C and 200°C." The claim language, specification, and prosecution history support this construction of the term. For example, the claim uses the phrase "at a temperature of from" to describe the temperature range. The patentee could have used the term "about" to describe the range but chose not to. The specification also supports the Court's construction. The specification describes a reaction that occurs "at an elevated temperature" and notes that the range of 100°C to 200°C is an example of such an elevated temperature. (*E.g.*, '014 patent at 2:23-24, 2:34-35.) The specification also gave another

[9] There is no indication in the intrinsic evidence that the claim requires a "bulk reaction," a term that appears nowhere in the patent. Nor does the claim require "deliberate" or intentional mixing without any intervening steps.

example of an "elevated temperature" range as 50°C to 120°C. (*Id*. at 3:19-20.) However, during prosecution, the applicant amended the claim, changing "at an elevated temperature" to "at a temperature of from 100 to 200°C"—a more precise range of temperatures. The Court will not now read in additional language to expand the meaning of this phrase beyond what is written in the claim and supported by the specification and prosecution history.

B. Claim 2 of the '014 Patent

Claim 2 of the '014 patent states:

> A **process according to claim 1 for the preparation of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one** by reaction of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one as the compound of formula (II) and 4-hydroxymethyl-5-methylimidazole as the compound of formula (III), the compound of formula (III) optionally being used in the form of the hydrochloride salt.

While this claim term was included in Prometheus' opening *Markman* brief as a term that Roxane sought to be construed, Roxane does not include it in its *Markman* briefs, nor do the parties include it in their Joint Claim Construction chart. Accordingly, the Court need not construe this term.

III. CONCLUSION

For the reasons set forth in this opinion, the Court construes the disputed claim terms of the '770 and '014 patent in accordance with the discussion above. An appropriate Order will issue.

s/ Faith S. Hochberg
Hon. Faith S. Hochberg, U.S.D.J.